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(54) Title: PROCESS FOR PREPARING NONRACEMIC CHIRAL ALCOHOLS

(57) Abstract: The present invention provides a catalyst system and a process for the preparation of a nonracemic chiral alcohol by hydrogenation of a ketone using the catalyst system, wherein the catalyst system comprises ruthenium, a nonracemic chiral diphosphine ligand, a bidentate amine ligand, and an organic base selected from alkylamidines, alkylguanidines, aminophosphazenes, and proazaphosphatranes.

PROCESS FOR PREPARING NONRACEMIC CHIRAL ALCOHOLS

FIELD OF THE INVENTION

[01] This invention relates generally to preparing nonracemic chiral alcohols. It more particularly relates to preparing nonracemic chiral alcohols by hydrogenation of ketones using transition metal catalysts comprising nonracemic chiral ligands. Nonracemic chiral alcohols are useful as pharmaceuticals and other bioactive products and as intermediates for the preparation of such products.

BACKGROUND OF THE INVENTION

[02] Ketones can be converted to racemic chiral alcohols by hydrogenation using certain catalyst systems of ruthenium, a phosphine ligand, a 1,2-diamine, and an alkaline base. Aromatic and heteroaromatic ketones can be hydrogenated to nonracemic chiral alcohols by using certain catalyst systems of ruthenium, an appropriate enantiomeric diphosphine ligand, an enantiomeric 1,2-diamine, and a base. *Angew. Chem. Int. Ed.*, vol. 40, (2001), 40-73 (a review with 211 references); U.S. Patent No. 5,763,688; *J. Am. Chem. Soc.*, vol. 117 (1995), 2675-2676; *J. Org. Chem.*, vol. 64 (1999), 2127-2129. U.S. Patent No. 5,763,688 states, "In the bases expressed by the general formula M^2Y, for example, M^2 is an alkali metal or an alkaline earth metal, and Y is a hydroxy group, alkoxy group, mercapto group or naphthyl group, and more specifically, applicable ones include KOH, $KOCH_3$, $KOCH(CH_3)_2$, $KC_{10}H_8$, $KOC(CH_3)_3$, LiOH, $LiOCH_3$, $LiOCH(CH_3)_2$, NaOH, $NaOCH_3$, $NaOCH(CH_3)_2$, as well as quaternary ammonium salt." It further states that, for solvent, "Since the product is alcohol, alcohol type solvents are preferable. More preferably, 2-propanol may be preferably used." The Examples of U.S. Patent No. 5,763,688 exemplify only KOH as the base and only 2-propanol as the solvent. *J. Am. Chem. Soc.*, vol. 117 (1995), 2675-2676, whose authors are inventors of U.S. Patent No. 5,763,688, further discusses this process of U.S. Patent No. 5,763,688 and states, "2-propanol is the solvent of choice. The reaction in methanol, ethanol, or *tert*-butylalcohol is much slower, while THF, dichoromethane, and toluene are not useable."

[03] Others have noted that ketones can be hydrogenated to nonracemic chiral alcohols using related catalyst systems formed with a racemic chiral 1,2-diamine. In their catalyst system, the active diastereomeric ruthenium catalyst is formed with the enantiomeric diphosphine ligand and the "matched" enantiomer of the racemic chiral 1,2-diamine. Interestingly, the diastereomeric ruthenium complex with the "unmatched

enantiomer of the racemic chiral 1,2-diamine, if it is formed, is relatively inactive. *Angew. Chem. Int. Ed.*, vol. 40, (2001), 40-73; European Patent Application 901 997; *J. Am. Chem. Soc.*, vol. 120 (1998), 1086-1087. European Patent Application 901 997, having inventors in common with U.S. Patent No. 5,763,688 states, "With regard to the base, an inorganic or a quaternary ammonium salt can be exemplified, preferably an alkali metal compound or an alkaline earth metal compound and a quaternary ammonium salt, more preferably an alkali metal or alkaline earth metal hydroxide or a salt thereof and a quaternary ammonium salt. Its illustrative examples include LiOH, LiOMe, LiOEt, $LiOCH(CH_3)_2$,. $LiOC(CH_3)_3$, NaOH, NaOMe, NaOEt, $NaOCH(CH_3)_2$, $NaOC(CH_3)_3$, KOH, $KOCH_3$, $KOCH(CH_3)_2$, $KOC(CH_3)_3$, $KC_{10}H_8$, and the like. A quaternary ammonium salt can also be used." It further states that, for solvent, "Because the product is an alcohol, alcohol solvents most preferred, and 2-propanol is particularly preferred." The Examples of European Patent Application 901 997 exemplify only KOH and $KOC(CH_3)_3$ as the base and only 2-propanol as main solvent. The other references cited above in this Background of the Invention section similarly use KOH or $KOC(CH_3)_3$ as the base and 2-propanol as main solvent.

[04] A catalyst system of ruthenium, the atropisomeric diphosphine (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (*S*-BINAP), achiral ethylenediamine, and potassium hydroxide in 2-propanol is reported to hydrogenate 1'-acetonaphthone to (*R*)-1-(1-naphthyl)ethanol in 57% enantiomeric excess. The corresponding catalyst system having enantiomeric (*S,S*)-1,2-diphenylethylenediamine instead of achiral ethylene diamine is reported to hydrogenate 1'-acetonaphthone under the same conditions to (*R*)-1-(1-naphthyl)ethanol in 97% enantiomeric excess. *Angew. Chem. Int. Ed.*, vol. 40, (2001), 40-73; *J. Am. Chem. Soc.*, vol. 117 (1995), 2675-2676.

[05] An attempt to provide a catalyst system of ruthenium, the atropisomeric diphosphine *S*-BINAP, enantiomeric (*S,S*)-1,2-diphenylethylenediamine, and 1,8-diaza-bicyclo[5.4.0]undec-7-ene as the base (in the place of the alkali base used in the references discussed above) in 2-propanol gave no catalytic activity for the hydrogenation of acetophenone. The addition of selected alkali metal salts of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate to this attempted catalyst system provided catalytic activity for the hydrogenation of acetophenone to nonracemic 1-phenethanol. The investigators conclude that alkali metal cations are required for the activity of this catalyst system. *Angew. Chem. Int. Ed.*, vol. 40, (2001), 3581-3585.

BRIEF SUMMARY OF THE INVENTION

[06] The present invention provides a catalyst system and a process for the preparation of a nonracemic chiral alcohol by hydrogenation of a ketone using the catalyst system, wherein the catalyst system comprises ruthenium, a nonracemic chiral diphosphine ligand, a bidentate amine ligand, and an organic base selected from alkylamidines, alkylguanidines, aminophosphazenes, and proazaphosphatranes, with the proviso that when the nonracemic chiral diphosphine is an atropisomeric diphosphine and the organic base is selected from alkylamidines, the catalyst system is essentially free of alkali metal salt. Preferably, the organic base is selected from alkylguanidines, aminophosphazenes, and proazaphosphatranes, and is most preferably selected from alkylguanidines. Surprisingly, these organic bases often provide greater enantioselectivity for the hydrogenation of a ketone to a nonracemic chiral alcohol as compared to the basic salts preferred in the teachings of the background references. Additionally, these organic bases allow the inventive process to be conducted with solvents other than the alcohol solvent preferred in the background references, including solvents such as dichloromethane and toluene and solvents in which the basic salts preferred in the background references are not soluble. Even more surprisingly, by using these organic bases to conduct the process in solvents other than alcohol solvents, increased enantioselectivities are often provided compared to those obtained when the process is conducted using alcohol solvents. Still more surprisingly, in certain embodiments, the chirality of the dominant enantiomer of the nonracemic alcohol product can be opposite that obtained with the otherwise identical catalyst system comprising a basic salt.

DETAILED DESCRIPTION OF THE INVENTION

[07] Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

[08] As used herein, the term "treating", "contacting" or "reacting" refers to adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product. "Side-reaction" is a reaction that does not ultimately lead to a production of a desired product.

[09] "Alkyl" means a linear saturated monovalent hydrocarbon radical or a branched saturated monovalent hydrocarbon radical or a cyclic saturated monovalent hydrocarbon radical, having the number of carbon atoms indicated in the prefix. For example, (C_1-C_6)alkyl is meant to include methyl, ethyl, *n*-propyl, 2-propyl, *tert*-butyl, pentyl, cyclopentyl, cyclohexyl and the like. For each of the definitions herein (*e.g.*, alkyl, alkenyl, alkoxy, aralkyloxy), when a prefix is not included to indicate the number of main chain carbon atoms in an alkyl portion, the radical or portion thereof will have twelve or fewer main chain carbon atoms. A divalent alkyl radical refers to a linear saturated divalent hydrocarbon radical or a branched saturated divalent hydrocarbon radical having the number of carbon atoms indicated in the prefix. For example, a divalent (C_1-C_6)alkyl is meant to include methylene, ethylene, propylene, 2-methylpropylene, pentylene, and the like.

[10] "Alkenyl" means a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical having the number of carbon atoms indicated in the prefix and containing at least one double bond. For example, (C_2-C_6)alkenyl is meant to include, ethenyl, propenyl, and the like.

[11] "Alkynyl" means a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical containing at least one triple bond and having the number of carbon atoms indicated in the prefix. For example, (C_2-C_6)alkynyl is meant to include ethynyl, propynyl, and the like.

[12] "Alkoxy", "aryloxy", " aralkyloxy", or "heteroaralkyloxy" means a radical -OR where R is an alkyl, aryl, aralkyl, or heteroaralkyl respectively, as defined herein, *e.g.*, methoxy, phenoxy, benzyloxy, pyridin-2-ylmethyloxy, and the like.

[13] "Aryl" means a monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 12 ring atoms which is substituted independently with one to four substituents, preferably one, two, or three substituents selected from alkyl, alkenyl, alkynyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino and heteroalkyl. More specifically the term aryl includes, but is not limited to, phenyl, biphenyl, 1-naphthyl, and 2-naphthyl, and the substituted derivatives thereof.

[14] "Aralkyl" refers to a radical wherein an aryl group is attached to an alkyl group, the combination being attached to the remainder of the molecule through the alkyl portion. Examples of aralkyl groups are benzyl, phenylethyl, and the like.

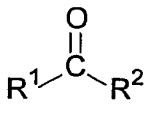
[15] "Heteroalkyl" means an alkyl radical as defined herein with one, two or three substituents independently selected from cyano, alkoxy, amino, mono- or di-alkylamino, thioalkoxy, and the like, with the understanding that the point of attachment

of the heteroalkyl radical to the remainder of the molecule is through a carbon atom of the heteroalkyl radical.

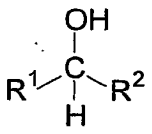
[16] "Heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring is optionally substituted independently with one to four substituents, preferably one or two substituents, selected from alkyl, alkenyl, alkynyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino and heteroalkyl. More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyridazinyl, pyrimidinyl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, tetrahydroquinolinyl, isoquinolyl, benzimidazolyl, benzisoxazolyl or benzothienyl, and the substituted derivatives thereof.

[17] "Hydrocarbyl" is used herein to refer to an organic radical, that can be an alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroalkyl or heteroaryl radical, or a combination thereof which is optionally substituted with one or more substituents generally selected from the groups noted above.

[18] In a general sense, the present invention provides a method for the preparation of a chiral alcohol of formula II (shown without stereochemistry) from a ketone of formula I. Suitable ketones for use in the present invention are those wherein R^1 and R^2 are different, and optionally, one or both of R^1 and R^2 have a chiral center.



I



II

[19] The symbols R^1 and R^2 in formulas I and II each independently represent a hydrocarbyl group that can be an acyclic, cyclic, or heterocyclic hydrocarbyl group, or a combination thereof. Additionally, each of the hydrocarbyl groups R^1 and R^2 can be saturated or unsaturated, including components defined above as alkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl groups, as well as combinations thereof. Still further, each of R^1 and R^2 can be optionally substituted with one or more substituents that do not interfere with the reaction chemistry of the

invention. In some embodiments, R^1 and R^2 are linked together in a cyclic structure. In a preferred combination of R^1 and R^2, R^1 is an optionally substituted alkyl group and R^2 is an optionally substituted aryl or heteroaryl group.

[20] R^1 and R^2 can also be, independently, chiral or achiral. As used herein, however, the adjective "chiral" in the term "chiral alcohol", specifically refers to the chirality at the carbon atom bearing each of R^1 and R^2, which chirality is produced by the hydrogenation of the keto group at that center. The term is not meant to refer to the chirality that may be present in either R^1 or R^2.

[21] The ruthenium, nonracemic chiral diphosphine ligand, and bidentate amine ligand components of the catalyst system can be provided to the reaction mixture individually to form the reactive catalyst complex *in situ* or they can be provided as preformed complexes. Preformed complexes of ruthenium with the diphosphine ligand, or the bidentate amine ligand, or both can be used.

[22] Examples of preformed complexes of the ruthenium with the diphosphine ligand include complexes represented by the formula RuX_2LY_n, wherein X represents a halogen atom or pseudo-halide group, preferably chloride or bromide, L represents the diphosphine ligand, Y represents a weakly coordinating neutral ligand, and n is an integer from 1 to 5. Examples of Y include trialkylamines, for examples triethylamine and tetramethylethylenediamine, and tertiary amides, for example dimethylformamide. Such complexes can be prepared by the reaction of the diphosphine ligand with a complex of the formula $[RuX_2(arene)]_2$, wherein examples of the arene include benzene, p-cymene, 1,3,5-trimethylbenzene, and hexamethylbenzene, in a solvent comprising Y.

[23] Examples of preformed complexes of the ruthenium with both the diphosphine ligand and bidentate amine ligand include complexes represented by the formula RuX_2LA, wherein A represents the bidentate amine ligand. Such complexes can be prepared by the reaction of the bidentate amine with a complex of the formula RuX_2LY_n as described above.

[24] The ruthenium component of the catalyst system, whether provided to the reaction mixture separately from the other components or used to form a preformed complex with the diphosphine ligand, the bidentate amine ligand, or both, can be provided by any ruthenium salt or complex capable of forming the active catalyst system in combination with the diphosphine ligand, the bidentate amine ligand, and the base. This can be determined by routine functional testing for ketone hydrogenation activity and enantioselectivity in the manner shown in the Examples. A preferred

source of the ruthenium component is a complex of the formula $[RuX_2(arene)]_2$ as defined above.

[25] Suitable nonracemic chiral diphosphine ligands for the present invention are bis-tertiary phosphines of the general formula $R^3R^4PR^aPR^5R^6$, wherein R^3, R^4, R^5, and R^6 are hydrocarbyl radicals, which may be the same or different, and R^a is a hydrocarbyl diradical, any of which may be optionally linked in one or more cyclic structures. Suitable hydrocarbyl groups R^3, R^4, R^5, R^6, and diradicals thereof for R^a, include acyclic, cyclic, or heterocyclic hydrocarbyl groups, or combinations thereof. Additionally, each of the hydrocarbyl groups R^3, R^4, R^5, R^6 and R^a can be saturated or unsaturated, including components defined above as alkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl groups, as well as combinations thereof. Still further, each of R^3, R^4, R^5, R^6 and R^a can be optionally substituted with one or more substituents that do not undesirably affect the reaction chemistry of the invention.

[26] The chirality of the diphosphine ligand may reside in one or more of the hydrocarbyl groups R^3, R^4, R^5, R^6, in the bridging hydrocarbyl radical R^a, at phosphorus when two hydrocarbyl radicals on phosphorus are different ($R^3 \neq R^4$, or $R^5 \neq R^6$, or both), or combinations thereof. Chirality in the bridging hydrocarbyl diradical R^a may be due to the presence of one or more stereogenic carbon atoms, or due to atropoisomerism.

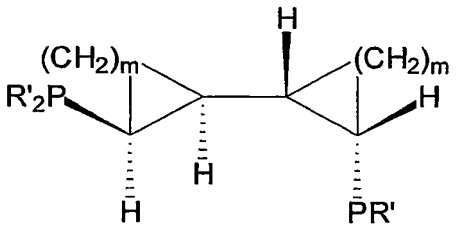
[27] Atropisomers do not comprise a stereogenic atom, but are chiral because of greatly hindered or prevented rotation about a single bond. Atropisomeric biaryl diphosphine ligands comprise a 1,1'-biaryl bond in the bridge between the phosphorus atoms, about which rotation is sterically prohibited and which are thereby chiral although lacking a stereogenic carbon or phosphorus atom. Examples of atropisomeric biaryl diphosphine ligands include, among others, the enantiomers of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), BINAP derivatives having one or more alkyl or aryl groups connected to one or both naphthyl rings, BINAP derivatives having one to five alkyl substituents on the phenyl rings bonded to phosphorus, for example 2,2'-bis-(di-p-tolylphosphino)-1,1'-binaphthyl (TolBINAP), 5,6,7,8,5',6',7',8'-octahydro-BINAP (H_8BINAP), 2,2'-bis(dicyclohexylphosphino)-6,6'-dimethyl-1,1'-biphenyl (BICHEP) , 2,2'-bis(diphenylphosphino)-6,6'-dimethyl-1,1'-biphenyl (BIPHEMP), 2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (MeOBIPHEP), [6,6'-(alkylene-α,ω-dioxy)biphenyl-2,2'-diyl]bis(diphenylphosphine) (Cn-TunaPhos; n=1,2,3,... for alkylene=methylene, 1,2-ethylene, 1,3-propylene,... , respectively), 5,5'-bis(diphenylphosphino)-4,4'-bi(benzodioxolyl) (SEGPHOS), and 2,2'-bis(diphenylphosphino)-3,3'-bi(benzo[b]thiophene) (BITIANP).

[28] Preferably, the nonracemic chiral diphosphine ligand is selected from nonracemic nonatropisomeric chiral diphosphine ligands, and more preferably, atropisomeric chiral substructures are not present in the nonracemic nonatropisomeric chiral diphosphine ligand. Most preferably, the nonracemic nonatropisomeric chiral diphosphine ligand comprises one or more stereogenic carbon atoms.

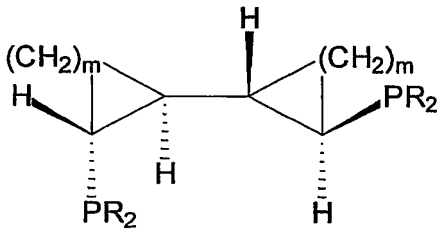
[29] Illustrative examples of nonracemic nonatropisomeric chiral diphosphine ligands are the enantiomers of 1,2-bis-(diphenylphosphino)propane (PROPHOS), 2,3-bis(diphenylphosphino)butane (CHIRAPHOS), 2,4-bis(diphenylphosphino)pentane (SKEWPHOS), 1-cyclohexyl-1,2-bis(diphenylphosphino)ethane (CYCPHOS), 1-substituted 3,4-bis(diphenyl-phosphino)pyrolidine (DEGPHOS), 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP), 3,4-O-isopropylidene-3,4-dihydroxy-2,5-bis(diphenylphosphino)hexane (DIOP*), 1-[1,2-bis-(diphenylphosphino)ferrocenyl]ethyldimethylamine (BPPFA), 1,2-bis[(o-methoxyphenyl)phenylphosphino]ethane (DIPAMP), 2,5-disubstituted 1,2-bis(phospholano)benzenes (DuPHOS), for example 1,2-bis(2,5-dimethyl-phospholano)benzene (Me-DuPHOS), substituted 1,2-bis(phospholano)ethylenes (BPE), for example 1,2-bis(2,5-dimethylphospholano)ethylene (Me-BPE), 1,2-bis-[3,4-benzoxy-2,5-dimethylphospholanyl]benzene (RoPhos), 1,2-bis-[3,4-O-isopropylidene-3,4-dihydroxy-2,5-dimethylphospholanyl]benzene (Me-KetalPhos), 1,1'-bis[3,4-O-iso-propylidene-3,4-dihydroxy-2,5-dimethyl-phospholanyl]ferrocene (Me-f-KetalPhos), 5,6-bis(diphenylphosphino)-2-norbornene (NORPHOS), N,N'-bis-(diphenylphosphino)-N,N'-bis(1-phenylethyl)ethylenediamine (PNNP), 2,2'-bis(diphenylphosphino)-1,1'-dicyclopentane (BICP), 1,2-bis-{2,5-disubstituted-7-phosphabicyclo[2.2.1]hept-7-yl}-benzenes (PennPhos), for example 1,2-bis-{2,5-dimethyl-7-phosphabicyclo[2.2.1]hept-7-yl}-benzene (Me-PennPhos) and 1,2-bis-{2,5-diisopropyl-7-phosphabicyclo[2.2.1]hept-7-yl}-benzene (iPr-PennPhos), and 1,2-bis{1-phosphatricyclo[3.3.0.0]undecan-1-yl}benzene (C5-Tricyclophos), and equivalents thereto that are recognized by those skilled in the art.

[30] Certain preferred nonracemic nonatropisomeric chiral diphosphine ligands comprise at least one, preferably at least two, and most preferably four, stereogenic carbon atoms in the hydrocarbyl diradical that connects the two phosphorus atoms (R^a in the formula above.). Illustrative examples of nonracemic nonatropisomeric chiral diphosphine ligands wherein the bridging hydrocarbyl diradical comprises a stereogenic carbon atom are the enantiomers of PROPHOS, CHIRAPHOS, SKEWPHOS, DIOP, DIOP*, and BICP ligands.

[31] Particularly preferred nonracemic nonatropisomeric chiral diphosphine ligands, wherein the bridging hydrocarbyl diradical comprises a stereogenic carbon atom, comprise a 2,2'-bis-(diorgano-phosphino)-1,1'-bis(cyclic) structure, wherein each cycle of the bridging bis(cyclic) diradical comprises three to eight carbon atoms, and wherein the 1, 1', 2, and 2' carbon atoms in the bis(cyclic) diradical are saturated. These ligands are described in detail in U.S. Patent No. 6,037,500, incorporated herein by reference. The preferred nonracemic diphosphine ligands comprising a 2,2'-bis-(diorgano-phosphino)-1,1'-bis(cyclic) structure are of the formulas III and IV and their enantiomers, in which m=1 to 6 and wherein each cycle of the bis(cyclic) structure may be unsubstituted as shown in formulas III and IV or further substituted with one or more substituents chosen from hydrocarbyl substituents and heteroatom containing substituents that do not interfere with the ketone hydrogenation chemistry, and wherein R' is a substituted or unsubstituted hydrocarbyl group selected from alkyl groups and aryl groups.

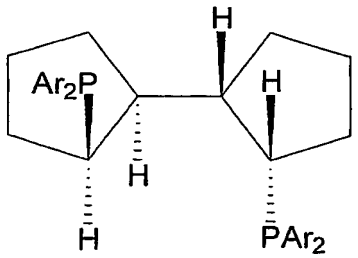


III



IV

[32] Particularly preferred nonracemic nonatropisomeric diphosphine ligands comprising a 2,2'-bis-(diorgano-phosphino)-1,1'-bis(cyclic) structure are of the formula V and its enantiomer, wherein Ar is an aryl group.



V

[33] Preferred aryl groups in formula V are phenyl (the BICP ligand) and mono-, di-, and trialkyl-phenyl, particularly wherein alkyl is methyl, for example 2,2'-bis[di(3,5-dimethylphenyl)phosphino]-1,1'-dicyclopentane (3,5-Me_8BICP).

[34] Suitable bidentate amine ligands comprise a primary amino group and another heteroatom-containing group that is capable of ligating to the ruthenium. Such

groups are known in the art, and include groups having a heteroatom selected from oxygen, nitrogen, sulfur, and phosphorus. Preferred bidentate amine ligands include diamines and amino-thioethers.

[35] The bidentate amine ligand may be achiral, racemic chiral, or nonracemic chiral. In certain inventive embodiments of the invention, the bidentate amine ligand is an achiral diamine.

[36] Suitable diamine ligands for the present invention are of the general formula $H_2NR^bNH_2$, wherein R^b is an hydrocarbyl diradical. Preferably, the hydrocarbyl diradical comprises at least two to fifty carbon atoms, more preferably at least three to fifty carbon atoms, still more preferably at least four to fifty carbon atoms, and most preferably at least six to fifty carbon atoms. Suitable hydrocarbyl diradicals for R^b include acyclic, cyclic, and heterocyclic hydrocarbyl diradicals, include saturated and unsaturated hydrocarbyl diradicals, include alkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl diradicals, and can be optionally substituted with one or more substituents that do not interfere with the reaction chemistry of the invention.

[37] Suitable chiral diamine ligands include the enantiomers and mixtures thereof of chiral derivatives of ethylenediamine, propylenediamines, butanediamines, cycloalkanediamines, and phenylenediamines. Illustrative examples include chiral stereoisomers of 1,2-diphenylethylenediamine, 1,2-cyclohexanediamine, 1,2-cycloheptanediamine, 2,3-dimethylbutanediamine, 1-methyl-2,2-diphenylethylenediamine, 1-isobutyl-2,2-diphenylethylenediamine, 1-isopropyl-2,2-diphenylethylenediamine, 1-methyl-2,2-di(p-methoxyphenyl)ethylenediamine, 1-isobutyl-2,2-di(p-methoxyphenyl)ethylenediamine, 1-isopropyl-2,2-di(p-methoxyphenyl-)ethylenediamine, 1-benzyl-2,2-di(p-methoxyphenyl)ethylenediamine, 1-methyl-2,2-dinaphthylethylenediamine, 1-isobutyl-2,2-dinaphthylethylenediamine, 1-isopropyl-2,2-dinaphthylethylenediamine, and equivalents thereto that are recognized by those skilled in the art, any of which may be substituted with one or more substituents that do not interfere with the reaction chemistry of the invention, and provided such substitution preserves the achirality of the diamine. Preferred chiral diamines are chiral stereoisomers of 1,2-diphenylethylenediamine and 1,2-cyclohexanediamine.

[38] Suitable achiral diamines may be achiral by comprising neither atropisomerism nor stereogenic carbon atoms or it may be achiral comprising a *meso* compound. That is, the achiral hydrocarbyl diradical may contain one or more pairs of stereogenic carbon atoms that are related in at least one of its conformations by a plane of symmetry. For example, while (*S*,*S*)- and (*R*,*R*)-1,2-diphenylethylenediamine

are chiral enantiomers, (*S*,*R*)-1,2-diphenylethylenediamine is an achiral *meso* compound.

[39] Illustrative examples of achiral diamines include ethylenediamine, 1,3-propylenediamine, 2-methyl-1,2-propylene-diamine, *meso*-2,3-butanediamine, *meso*-1,2-cyclopentanediamine, *meso*-1,2-cyclo-hexane-diamine, *meso*-1,2-cyclo-heptane-diamine, *meso*-1,2-diphenylethylenediamine, *meso*-2,3-dimethyl-butane-1,2-diamine, 1,2-phenylenediamine, 2-aminobenzyl-amine, 1,8-diaminonaphthalene, and equivalents thereto that are recognized by those skilled in the art, any of which may be substituted with one or more substituents that do not interfere with the reaction chemistry of the invention, and provided such substitution preserves the achirality of the diamine.

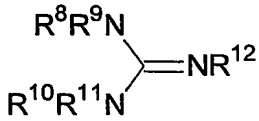
[40] Preferred achiral diamines are selected from 1,2-alkylenediamine compounds, 1,2-phenylenediamine compounds and 1,8-diamino-naphthalene compounds, which may be substituted or unsubstituted. Suitable substituents include alkyl (e.g. 4,5-dimethyl-1,2-phenylene-diamine), benzo (e.g. 9,10-diaminophenanthrene), and alkoxy (e.g, 1,3-benzodioxole-5,6-diamine).

[41] Suitable amino-thioether ligands for the present invention are of the general formula $H_2NR^cSR^7$, wherein R^7 is a hydrocarbyl radical and R^c is a hydrocarbyl diradical and which may be optionally linked in a cyclic structure. Suitable hydrocarbyl groups R^7 and diradicals thereof for R^c include acyclic, cyclic, and heterocyclic hydrocarbyl groups, include saturated and unsaturated hydrocarbyl groups, include alkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl groups, and can be optionally substituted with one or more substituents that do not undesirably the reaction chemistry of the invention. The amino-thioether ligand may be achiral, racemic chiral, or nonracemic chiral, preferably achiral.

[42] Preferred amino-thioether ligands are selected from 2-(alkylthio)ethylamines, 2-(alkylthio)anilines, and equivalents thereto that are recognized by those skilled in the art. Most preferred are 2-(alkylthio)anilines. Preferably the alkyl group therein is selected from C_1 to C_4 alkyl groups. Most preferred are methyl and ethyl. Illustrative examples include 2-(methylthio)aniline and 2-(ethylthio)aniline.

[43] Turning next to the organic bases suitable for use in the present methods, those bases selected from alkylamidines, alkylguanidines, aminophosphazenes and proazaphosphatranes have been found particularly attractive as providing, in some instances, greater enantioselectivity and utility with solvent systems other than the alcohols used in related processes.

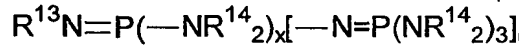
[44] Suitable alkylguanidines have the general formula VI, wherein R^8, R^9, R^{10}, R^{11}, and R^{12} are independently selected from hydrogen and alkyl groups, with the proviso that at least one of R^8, R^9, R^{10}, R^{11}, and R^{12} is an alkyl group.



VI

[45] Preferably the alkylguanidine comprises two alkyl groups, more preferably three alkyl groups, even more preferably four alkyl groups, and most preferably five alkyl groups. Any of the alkyl groups R^8, R^9, R^{10}, R^{11}, and R^{12} may be optionally linked in one or more cyclic structures. An illustrative example of a suitable tetraalkylguanidine base is 1,5,7-triazabicyclo[4.4.0]dec-5-ene and tetramethylguanidine. Illustrative examples of suitable pentalkylguanidines are 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene and tetramethyl-2-t-butylguanidine.

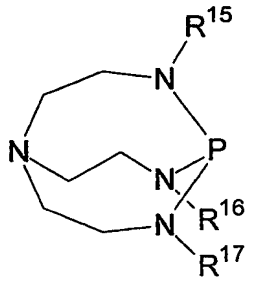
[46] Suitable aminophosphazenes have the general formula VII, wherein R^{13} is selected from hydrogen and alkyl groups, R^{14} is an alkyl group and the two R^{14} groups on each $-NR^{14}_2$ group may optionally be linked in a cyclic structure, and x is an integer from zero to three, preferably 3.



VII

[47] Illustrative examples of suitable aminophosphazenes include N,N,N',N',N",N"-hexa-methyl-phosphorimidic triamide (R^{13}=H, R^{14}=methyl, x=3), N"'-t-butyl-N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide (R^{13}=t-butyl, R^{14}=methyl, x=3), (t-butyl-imino)-tris(pyrrolidino)-phosphorane (R^{13}=t-butyl, $-NR^{14}_2$=pyrrolidino, x=3), N"'-[N-ethyl-P,P-bis-(dimethyl-amino)phosphinimyl]-N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide (R^{13}=ethyl, R^{14}=methyl, x=2), and t-butyl-tris[tris(dimethyl-amino)-phosphoranylidene]phosphorimidic triamide (R^{13}=t-butyl, R^{14}=methyl, x=0).

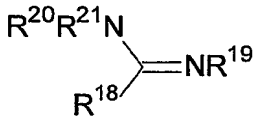
[48] Suitable proazaphosphatranes are described in U.S. Patent No. 5,051,533 and have the general formula VIII, wherein R^{15}, R^{16}, and R^{17} are independently selected from hydrogen and alkyl groups.



VIII

[49] Preferably R^{15}, R^{16}, and R^{17} are selected from C_1 to C_8 alkyl groups, most preferably methyl. An illustrative preferred proazaphosphatrane is 2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (R^{15}=R^{16}=R^{17}=methyl).

[50] Suitable alkylamidines have the general formula IX wherein R^{18}, R^{19}, and R^{20} are independently selected from alkyl groups and R^{21} is selected from hydrogen and alkyl groups. Preferably, R^{21} is selected from alkyl groups.



IX

[51] Any of the alkyl groups R^{18}, R^{19}, R^{20}, and R^{21} may be optionally linked in one or more cyclic structures. An illustrative example of a suitable alkylamidine base is 1,5-diazabicyclo[4.3.0]non-5-ene.

[52] Preferably, the organic base is selected from alkylguanidines, aminophosphazenes, and proazaphosphatranes. More preferably, the organic base is an alkylguanidine, most preferably selected from tetraalkylguanidines and pentaalkylguanidines.

[53] Preferably, the catalyst system is essentially free of alkali metal salt. The invention includes the proviso that for embodiments wherein an alkylamidine base is used in combination with a nonracemic atropisomeric diphosphine ligand, the catalyst system is essentially free of alkali metal salt. The phrase "essentially free of alkali metal salt" means that the concentration of the alkali metal salt is not sufficient to significantly increase the activity of the catalyst system. This can be readily determined experimentally. Preferably the catalyst system is free of alkali metal salt.

[54] The components of the catalyst system are each present in a catalytic amount, meaning less than stoichiometric relative to the ketone reactants. The minimum amount of the catalyst system relative to the ketone reactant may depend on the activity of the specific catalyst system composition, the specific ketone to be reacted, the hydrogen pressure, the gas-liquid mixing characteristics of the reaction

vessel, the reaction temperature, the concentrations of the reactants and catalyst system components in the solution, and the maximum time allowed for completion of the reaction, and can be readily determined by routine experimentation. In typical embodiments, the mole ratio of the ruthenium component of the catalyst system to the ketone reactant is in the range from about 1/100 to about 1/100,000, preferably in the range from about 1/500 to about 1/10,000.

[55] The mole ratio of the nonracemic diphosphine ligand to the ruthenium in the catalyst system is typically in the range from about 0.5 to about 2.0, preferably from about 0.8 to about 1.2, and most preferably is about 1. The mole ratio of the bidentate amine ligand to the ruthenium in the catalyst system is typically in the range from about 1 to about 50, and preferably from about 5 to about 20. The mole ratio of the base to the ruthenium in the catalyst system is typically in the range from about 1 to about 100, and preferably from about 5 to about 50.

[56] The hydrogenation reaction may be conducted without solvent when the ketone itself is a liquid at the reaction temperature and capable of dissolving the catalyst system. More typically, the hydrogenation reaction is conducted in a solvent system that is capable of dissolving the catalyst system and is reaction-inert. The term solvent system is used to indicate that a single solvent or a mixture of two or more solvents can be used. The term reaction-inert it used to mean that the solvent system does not react unfavorably with the reactants, products, or the catalyst system.

[57] The term reaction-inert does not mean that the solvent does not participate productively in the desired reaction. For example, while not wishing to be bound by theory, it is believed that alcohol solvents level organic bases selected from the preferred alkylguanidines, aminophosphazenes, or proazaphosphatranes. That is, these bases deprotonate the alcohol to form an alkoxide base in the reaction solution. However, the mere formation of an alkoxide base *in situ* cannot explain the often greater enantioselectivity in the ketone hydrogenation reaction that is provided by the organic bases of the present invention compared to the basic alkoxide salts preferred in the teachings of the background references. Also, the organic bases of the present invention allow the inventive process to be conducted using solvents other than alcohol solvents, including solvents in which the basic alkoxide salts preferred in the background references are not soluble.

[58] The solvent system need not bring about complete solution of the ketone reactant or the chiral alcohol product. The ketone reactant may be incompletely dissolved at the beginning of the reaction or the chiral alcohol product may be incompletely dissolved at the end of the reaction, or both.

[59] Representative solvents are aromatic hydrocarbons such as benzene, toluene, xylene; aliphatic hydrocarbons such as pentane, hexane, heptane; halogen-containing hydrocarbon solvents such as dichloromethane and chlorobenzene; alkyl ethers, polyethers, and cyclic ethers such as methyl-t-butyl-ether, dibutylether, diethoxymethane, 1,2-dimethoxyethane, and tetrahydrofuran; ester solvents such as ethyl acetate, organic solvents containing heteroatoms such as acetonitrile, DMF and DMSO; and alcohol solvents such as methanol, ethanol, 2-propanol, t-butanol, benzyl alcohol and the like; and mixtures thereof.

[60] In typical embodiments, the reaction is suitably conducted at a temperature from about -30°C to about 100°C, more typically from about 0°C to about 50°C, and most typically from about 20°C to about 40°C.

[61] The terms "hydrogenating" and "hydrogenation" refer to reacting the ketone with a source of hydrogen atoms under appropriate conditions so that two hydrogen atoms are added to the carbonyl group of the ketone to produce the hydroxyl group of the chiral alcohol. The source of hydrogen atoms may be molecular hydrogen (H_2), a hydrogen donating organic or inorganic compound, or mixtures thereof. Preferably the source of hydrogen atoms includes molecular hydrogen. Hydrogen donating compounds are compounds capable of donating hydrogen atoms via the action of the catalyst system. Compounds capable of donating hydrogen atoms for transfer hydrogenation reactions using ruthenium catalysts are known in the art, and include alcohols such as methanol, ethanol, *n*-propanol, isopropanol, butanol and benzyl alcohol, formic acid and salts thereof, unsaturated hydrocarbons and heterocyclic compounds having in part a saturated C-C bond such as tetralin, cyclohexane, and cyclohexadiene, hydroquinone, phosphorous acid, and the like. Among hydrogen donating compounds, alcohols are preferred and isopropanol is most preferred.

[62] The hydrogen pressure in the reaction is typically at least about 1 atm, and typically in the range from about 1 atm to about 100 atm. More typically, the hydrogen pressure is in the range from about 5 atm to about 20 atm.

[63] The reaction rate and time to completion are dependent on the identities of the ketone reactant and the catalyst components, their absolute concentrations and relative ratios, the temperature, the hydrogen pressure, the gas-liquid mixing provided, and the other reaction conditions. Typically, the reaction is allowed to continue for sufficient time to complete the conversion of the ketone reactant. For typical ketone reactants, using the preferred catalyst systems described and the preferred reaction conditions described herein, the reaction is typically completed in a period of time in the

range from about a few minutes to about 24 hours, more typically in the range from about 1 hour to about 10 hours.

[64] The nonracemic chiral alcohol product has, by definition, a stereomeric excess greater than zero. In preferred embodiments, the nonracemic chiral alcohol is formed in at least about 50% stereomeric excess, more preferably at least about 60%, still more preferably at least about 70%, still again more preferably at least about 80%, and most preferably at least about 90%. These stereomeric excesses refer to the chirality at the hydroxyl-bearing carbon of the alcohol group generated by the hydrogenation of the ketone group. When the ketone is achiral, the chiral alcohol can be one of two enantiomers, and the enantiomer excess (e.e.) is the measure of stereomeric excess. When the ketone reactant is already chiral, the chiral alcohol product is a diastereomer, and diastereomeric excess (d.e.) is the formally appropriate measure of stereomeric excess. Accordingly, the term "nonracemic diastereomer" when used to refer to a nonracemic chiral alcohol product, refers to a product with an excess of one diastereomer vs. its diastereomer with the opposite chirality at the hydroxyl-bearing carbon. Preferably, the nonracemic diastereomer is produced in at least about 50% d.e., more preferably at least about 60% d.e., still more preferably at least about 70% d.e., still again more preferably at least about 80% d.e., and most preferably at least about 90% d.e.

EXAMPLES OF THE INVENTION

[65] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following specific examples are intended merely to illustrate the invention and not to limit the scope of the disclosure or the scope of the claims in any way whatsoever.

Preparation 1

[66] Preparation of [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n]: To 7.5 mg (30 microgram-atom Ru) [$RuCl_2$(benzene)]$_2$ and 16.2 mg (32 micromole) (*R*,*R*,*R*,*R*)-2,2'-bis-(diphenylphosphino)-1,1'-dicyclopentane (*R*,*R*,*R*,*R*-BICP) in a 200 mL Schlenk flask under nitrogen was added 10 mL anhydrous, deaerated dimethylformamide (DMF). The resulting orange solution was heated at 130°C for 30 minutes, then evaporated to dryness at 130°C under vacuum (10 mmHg). The resulting orange-red solid residue, comprising [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n], was further dried at 80°C under vacuum for at least an additional hour. A stock solution of 250 micromolar [$RuCl_2$((*R*,*R*,*R*,*R*-BICP)(DMF)n] in isopropanol was prepared by dissolving the solid residue in 120 mL anhydrous, deaerated isopropanol and stored under nitrogen.

[67] This general procedure was used for the preparation of the other [$RuCl_2$(diphosphine)(DMF)n] complexes and the solutions thereof used in the following Examples.

Example 1

[68] This Example illustrates the process of the invention wherein acetophenone is hydrogenated to nonracemic 1-phenethanol using a ruthenium catalyst system comprising a nonracemic diphosphine ligand, a bidentate amine ligand and a pentaalkylguanidine base.

[69] In a dry nitrogen-filled glovebox, a 20-ml glass reaction vial was charged with 5 mL 250 micromolar (1.25 micromole) [$RuCl_2$((*R*,*R*,*R*,*R*-BICP)(DMF)n] in isopropanol, 5 mL isopropanol, and 125 microliter 0.1M (12.5 micromole) ethylene-diamine in isopropanol. After stirring for several minutes, 73 microliter (625 micromole) acetophenone was added, followed by 0.50 mL 0.1 M (50 micromoles) tetramethyl-2-t-butylguanidine in isopropanol. The glass reaction vial containing the resulting mixture was sealed in an autoclave, which was then removed from the glovebox. The gas phase in the autoclave was replaced by hydrogen at 18 bar and the reaction mixture was stirred at room temperature for 6 hours under 17-18 bar hydrogen. After releasing the hydrogen pressure, 1 ml of the resulting reaction solution was eluted through a short column of silica gel with 9 mL methanol. Chiral gas chromatographic analysis of the eluate showed 100% conversion of the acetophenone to give *S*-1-phenethanol with 77% e.e.

Comparative Example 1

[70] This Comparative Example shows the result substituting an alkoxide salt for the alkylguanidine base exemplified in Examples 1.

[71] The procedure was the identical to Example 1 with the exemption that 0.50 mL 0.1 M (50 micromoles) sodium isopropoxide was used instead of the tetramethyl-2-t-butylguanidine solution. The analysis showed 100% conversion of the acetophenone to give *S*-1-phenethanol with 51% e.e.

[72] By comparison, Example 1 shows that the enantioselectivity for hydrogenation of acetophenone is substantially greater with the otherwise identical catalyst comprising an alkylguanidine base.

Examples 2-7 and Comparative Examples 2-7

[73] These Examples illustrate the process of the invention wherein acetophenone is hydrogenated to nonracemic 1-phenethanol using catalysts systems

comprising various diamine ligands, including achiral diamines and enantiomers of chiral diamines, in combination with a pentaalkylguanidine base. The Comparative Examples show the corresponding results obtained by substituting an alkoxide salt for the alkylguanidine base.

[74] The procedure was identical to Example 1 with the exemptions that an equimolar amount of the diamine ligand listed in Table 1 was substituted for the ethylenediamine, the reaction mixture was stirred under hydrogen for the time shown in Table 1, and for the Comparative Examples, an equimolar amount of sodium isopropoxide was substituted for the tetramethyl-2-t-butylguanidine. In each example, the analysis showed the conversion of the acetophenone was 100%. Table 1 gives the diamine ligand, the base, the reaction time, and the enantiomeric excess of the *S*-1-phenethanol product.

Table 1

Example.	Diamine	base	Time (hrs)	e.e. (%)
1	Ethylenediamine	tetramethyl-2-t-butylguanidine	6	77
Comp.1	Ethylenediamine	sodium isopropoxide	6	51
2	1,3-propylenediamine	tetramethyl-2-t-butylguanidine	4	78
Comp. 2	1,3-propylenediamine	sodium isopropoxide	6	77
3	4,5-dimethyl-1,2-phenylenediamine	tetramethyl-2-t-butylguanidine	10	77
Comp. 3	4,5-dimethyl-1,2-phenylenediamine	sodium isopropoxide	6	71
4	1,8-naphthalenediamine	tetramethyl-2-t-butylguanidine	4	86
Comp. 4	1,8-naphthalenediamine	sodium isopropoxide	8	86
5	*R,R*-1,2-cyclohexanediamine	tetramethyl-2-t-butylguanidine	6	68
Comp. 5	*R,R*-1,2-cyclohexanediamine	sodium isopropoxide	6	62
6	*S,S*-1,2-cyclohexanediamine	tetramethyl-2-t-butylguanidine	6	14
Comp. 6	*S,S*-1,2-cyclohexanediamine	sodium isopropoxide	6	3
7	*meso*-1,2-cyclohexanediamine	tetramethyl-2-t-butylguanidine	12	71
Comp. 7	*meso*-1,2-cyclohexanediamine	sodium isopropoxide	6	67

[75] The results in Table 1 show that the enantioselectivity for hydrogenation of acetophenone is at least as good as and in many cases better for the catalyst system comprising the pentaalkylguanidine base compared to the otherwise identical catalyst system comprising an the alkoxide salt for the base.

Examples 8-16 and Comparative Examples 8-16

[76] These Examples illustrate the process of the invention wherein 2-acetyl-thiophene to nonracemic 1-(2-thienyl)ethanol using catalysts systems comprising

various diamine ligands, including achiral diamines and enantiomers of chiral diamines, in combination with a pentaalkylguanidine base. The Comparative Examples show the corresponding results obtained by substituting an alkoxide salt for the alkylguanidine base.

[77] The procedure was identical to Example 1, with the exceptions that 68 microliter (625 micromole) 2-acetylthiophene was reacted instead of the acetophenone, an equimolar amount of the diamine ligand listed in Table 2 was substituted for the ethylenediamine, the reaction mixture was stirred under hydrogen for the time shown in Table 2, and for the Comparative Examples, an equimolar amount of sodium isopropoxide was substituted for the tetramethyl-2-t-butylguanidine. In each example, the analysis showed the conversion of the acetophenone was 100%. Table 2 gives the diamine ligand, the base, the reaction time, and the enantiomeric excess of the 1-(2-thienyl)ethanol product.

Table 2

Example	Diamine	base	Time (hrs)	e.e. (%)
8	Ethylenediamine	tetramethyl-2-t-butylguanidine	4	86
Comp. 8	Ethylenediamine	sodium isopropoxide	4	56
9	1,3-propylenediamine	tetramethyl-2-t-butylguanidine	4	85
Comp. 9	1,3-propylenediamine	sodium isopropoxide	4	82
10	4,5-dimethyl-1,2-phenylenediamine	tetramethyl-2-t-butylguanidine	4	84
Comp. 10	4,5-dimethyl-1,2-phenylenediamine	sodium isopropoxide	4	84
11	1,8-naphthalenediamine	tetramethyl-2-t-butylguanidine	4	86
Comp. 11	1,8-naphthalenediamine	sodium isopropoxide	4	85
12	*R,R*-1,2-cyclohexanediamine	tetramethyl-2-t-butylguanidine	4	87
Comp. 12	*R,R*-1,2-cyclohexanediamine	sodium isopropoxide	4	72
13	*S,S*-1,2-cyclohexanediamine	tetramethyl-2-t-butylguanidine	6	62
Comp. 13	*S,S*-1,2-cyclohexanediamine	sodium isopropoxide	6	16
14	*meso*-1,2-cyclohexanediamine	tetramethyl-2-t-butylguanidine	4	90
Comp. 14	*meso*-1,2-cyclohexanediamine	sodium isopropoxide	4	81
15	*R*-1,2-propylenediamine	tetramethyl-2-t-butylguanidine	6	89
Comp. 15	*R*-1,2-propylenediamine	sodium isopropoxide	6	77
16	2-aminobenzylamine	tetramethyl-2-t-butylguanidine	6	57
Comp. 16	2-aminobenzylamine	sodium isopropoxide	6	54

[78] The results in Table 2 show that the enantioselectivity for hydrogenation of 2-acetylthiophene is at least comparable and in many cases significantly better for the catalyst system comprising the pentaalkylguanidine base compared to the otherwise identical catalyst system comprising an the alkoxide salt for the base.

Example 17

[79] This Example illustrates the process of the invention wherein acetophenone is hydrogenated to nonracemic 1-phenethanol using a ruthenium catalyst system comprising a nonracemic diphosphine ligand, a bidentate amine ligand and a tetraaalkylguanidine base.

[80] The procedure was the identical to Example 1 with the exemptions that 0.50 mL 0.1 M (50 micromoles) 1,5,7-triazabicyclo[4.4.0]dec-5-ene was used instead of the tetramethyl-2-t-butylguanidine solution and the reaction time was 12 hours. The analysis showed 100% conversion of the acetophenone to give *S*-1-phenethanol with 83% e.e.

[81] By comparison with Comparative Example 1, this Example shows that the enantioselectivity for hydrogenation of acetophenone is substantially greater with the catalyst system comprising the tetraalkylguanidine base compared to the otherwise identical catalyst system comprising an the alkoxide salt for the base.

Examples 18-25

[82] These Examples show the process of the invention for hydrogenation of 2-acetylthiophene to nonracemic 1-(2-thienyl)ethanol using a various bases selected from alkylamidines, alkylguanidines and aminophosphazenes with ethylenediamine as the bidentate amine ligand.

[83] The procedure was identical to Examples 8 with the exceptions that an equal molar amount of the base shown in Table 3 was substituted for the tetramethyl-2-t-butylguanidine and the reaction mixtures were stirred under hydrogen for the time shown in Table 2. Table 2 gives the base, the reaction time, the conversion of the 2-acetylthiophene, and the enantiomeric excess of the *S*-1-(2-thienyl)ethanol product.

Table 3				
Example	Base	Time (hrs)	Conv. (%)	e.e. (%)
Comp. 8	sodium isopropoxide	4	100	56
8	tetramethyl-2-t-butylguanidine	6	100	86
18	1,5-diazabicyclo[4.3.0]non-5-ene	12	8	89
19	1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	100	88
20	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	95	90
21	N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	6	88	89
22	N"'-*t*-butyl-N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	12	100	81
23	(t-butyl-imino)-tris(pyrrolidino)phosphorane	12	100	61
24	N"'-[N-ethyl-P,P-bis(dimethylamino)phosphinimyl]-N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	12	100	51
25	t-butyl-tris[tris(dimethylamino)phosphoranylidene]-phosphorimidic triamide	6	100	51

[84] By comparison to Comparative Example 8, these Examples demonstrate that a variety of bases selected from alkylamidines, alkylguanidines and aminophosphazenes provide enantioselectivities at least comparable, and in some instances substantially superior to that provided by a basic salt (sodium isopropoxide) as the base in the inventive catalyst systems using ethylene diamine as the achiral diamine ligand.

Examples 26-32

[85] These Examples show the process of the invention for hydrogenation of 2-acetylthiophene to nonracemic 1-(2-thienyl)ethanol using a various bases selected from alkylguanidines and aminophosphazenes with *meso*-1,2-cyclohexanediamine as the bidentate amine ligand.

[86] The procedure was identical to Example 14 with the exceptions that an equal molar amount of the base shown in Table 4 was substituted for the tetramethyl-2-t-butylguanidine and the reaction mixtures were stirred under hydrogen for the time shown in Table 4. Table 4 gives the base, the reaction time, the conversion of the 2-acetylthiophene, and the enantiomeric excess of the *S*-1-(2-thienyl)ethanol product.

Table 4				
Example	Base	Time (hrs)	Conv. (%)	e.e. (%)
Comp. 14	sodium isopropoxide	4	100	81
14	tetramethyl-2-t-butylguanidine	4	84	90
26	1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	56	90
27	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	34	91
28	N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	6	30	90
29	N"'-*t*-butyl-N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	12	100	90
30	(t-butyl-imino)-tris(pyrrolidino)phosphorane	12	100	85
31	N"'-[N-ethyl-P,P-bis(dimethylamino)phosphinimyl]-N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	12	100	79
32	t-butyl-tris[tris(dimethylamino)phosphoranylidene]-phosphorimidic triamide	12	100	80

[87] By comparison to Comparative Example 14, these Examples demonstrate that a variety of bases selected from alkylguanidines and aminophosphazenes provide enantioselectivities at least comparable, and in some superior, to that provided by a basic salt (sodium isopropoxide) as the base in the inventive catalyst systems.

Examples 33-36

[88] These Examples show the process of the invention for hydrogenation of 2-acetylthiophene to nonracemic 1-(2-thienyl)ethanol using various bases selected from alkylguanidines and aminophosphazenes in combinations with enantiomers of chiral 1,2-cyclohexanediamine as the bidentate amine ligand.

[89] The procedure was identical to Examples 12 and 13, for *R,R*- and *S,S*-1,2-cyclohexanediamine respectively, with the exceptions that an equal molar amount of the base shown in Table 5 was substituted for the tetramethyl-2-t-butylguanidine and the reaction mixtures were stirred under hydrogen for the time shown in Table 5. Table 5 gives the chirality of the 1,2-cyclohexane diamine, the base, the reaction time, the conversion of the 2-acetylthiophene, and the enantiomeric excess of the *S*-1-(2-thienyl)ethanol product.

Table 5					
Example	**c-hexane diamine**	**Base**	**Time (hrs)**	**Conv. (%)**	**e.e. (%)**
Comp. 12	*R,R*-	sodium isopropoxide	4	100	72
12	*R,R*-	tetramethyl-2-t-butylguanidine	4	100	87
33	*R,R*-	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	99	92
34	*R,R*-	N'''-*t*-butyl-N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide	12	100	85
Comp. 13	*S,S*-	sodium isopropoxide	6	100	16
13	*S,S*-	tetramethyl-2-t-butylguanidine	6	100	62
35	*S,S*-	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	92	72
36	*S,S*-	N'''-*t*-butyl-N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide	12	100	56

[90] The results in Table 5 demonstrate, for each enantiomer of chiral 1,2-cylcohexanediamine, that bases selected from alkylguanidines and aminophosphazenes can provide substantially greater enantioselectivities to that provided by an alkoxide salt.

[91] In all these Examples, the chirality of the dominant enantiomer of the nonracemic alcohol product is the same, *S*, showing that it is controlled by the chirality of the diphosphine enantiomer. Among these results, the chirality of the 1,2-cyclohexanediamine affects only the degree of enantioselectivity toward the *S*-alcohol. Comparisons between the results that use the same base consistently show that that the *R,R*-1,2-cyclohexanediamine is matched to the chirality of the *R,R,R,R*-BICP, their combination giving higher enantioselectivities than the combination of the *S,S*-1,2-cyclohexanediamine with *R,R,R,R*-BICP.

[92] Surprisingly, Example 35 shows that the unmatched combination of *S,S*-1,2-cyclohexanediamine with *R,R,R,R*-BICP when used with an alkylguanidine base can provide in an enantioselectivity on par with the matched combination of *R,R*-1,2-cyclohexanediamine with *R,R,R,R*-BICP when used with the alkoxide salt base (Comparative Example 12).

Examples 37-45 and Comparative Examples 15 and 17

[93] These Examples show the process of the invention for hydrogenation of 2-acetylthiophene to nonracemic 1-(2-thienyl)ethanol using various bases selected from alkylguanidines and aminophosphazenes in combinations with the enantiomers of 1,2-propylenediamine as the bidentate amine ligand.

[94] The procedure was identical to Example 15 with the exceptions that *S*-1,2-propylenediamine was substituted for *R*-1,2-propylenediamine in some of the

Examples, an equal molar amount of the base shown in Table 6 was substituted for the tetramethyl-2-t-butylguanidine, and the reaction mixtures were stirred under hydrogen for the time shown in Table 6. Table 6 gives the chirality of the 1,2-propylenediamine, the base, the reaction time, the conversion of the 2-acetylthiophene, and the enantiomeric excess of the *S*-1-(2-thienyl)ethanol product.

Table 6

Example	diamine chirality	Base	Time (hrs)	Conv. (%)	e.e. (%)
Comp. 17	*S*-	sodium isopropoxide	6	100	35
37	*S*-	tetramethyl-2-t-butylguanidine	6	85	70
38	*S*-	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	88	75
Comp. 15	*R*-	sodium isopropoxide	6	100	77
15	*R*-	tetramethyl-2-t-butylguanidine	6	100	89
39	*R*-	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	100	94
40	*R*-	1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	100	93
41	*R*-	N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	6	96	94
42	*R*-	N"'-*t*-butyl-N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	12	100	89
43	*R*-	(t-butyl-imino)-tris(pyrrolidino)phosphorane	12	100	81
44	*R*-	N"'-[N-ethyl-P,P-bis(dimethylamino)-phosphinimyl]-N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	12	100	76
45	*R*-	t-butyl-tris[tris(dimethylamino)-phosphoranylidene]phosphorimidic triamide	6	100	76

[95] The results in Table 6 demonstrate, for each enantiomer of 1,2-propylenediamine, that bases selected from alkylguanidines and aminophosphazenes can provide substantially greater enantioselectivities to that provided by an alkoxide salt.

[96] In all these Examples, the chirality of the dominant enantiomer of the nonracemic alcohol product is the same, *S*, showing that it is controlled by the chirality of the diphosphine enantiomer. Among these results, the chirality of the 1,2-propylenediamine affects only the degree of enantioselectivity toward the *S*-alcohol. Comparisons between the results that use the same base consistently show that that the *R*-1,2-propylenediamine is matched to the chirality of the *R,R,R,R*-BICP, their combination giving higher enantioselectivities than the combination of the *S*-1,2-propylenediamine with *R,R,R,R*-BICP.

[97] Surprisingly, Example 38 shows that the unmatched combination of *S*-1,2-propylenediamine with *R,R,R,R*-BICP when used with an alkylguanidine base can provide in an enantioselectivity comparable with the matched combination of *R*-1,2-propylenediamine with *R,R,R,R*-BICP when used with the alkoxide salt base (Comparative Example 15).

Examples 46-50 and Comparative Examples 18-22

[98] These Examples show the hydrogenation of various ketones using either the tetraalkylguanidine 1,5,7-triazabicyclo[4.4.0]dec-5-ene (the Examples) or sodium isopropoxide (the Comparative Examples) in combination with ethylenediamine as the bidentate amine ligand.

[99] The procedure was identical to Example 1 with the exceptions that 625 micromole of the ketone shown in Table 7 was reacted instead of the acetophenone, an equimolar amount of either 1,5,7-triazabicyclo[4.4.0]dec-5-ene or sodium isopropoxide was substituted for the tetramethyl-2-t-butylguanidine, and the reaction mixture was stirred under hydrogen for the time shown in Table 7. In each example, the analysis showed the conversion of the ketone was 100% and that the chirality of the product alcohol was predominantly *S*. Table 7 gives the ketone, the base, the reaction time, and the enantiomeric excess of the *S*-alcohol product.

Table 7

Example	ketone	base	Time (hrs)	e.e. (%)
2	acetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	83
Comp. 1	acetophenone	sodium isopropoxide	6	51
8	2-acetylthiophene	1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	88
Comp. 8	2-acetylthiophene	sodium isopropoxide	4	56
46	2'-acetonaphthone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	83
Comp. 18	2'-acetonaphthone	sodium isopropoxide	9	64
47	2-acetylbenzothiophene	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	82
Comp. 19	2-acetylbenzothiophene	sodium isopropoxide	12	68
48	2-acetylfuran	1,5,7-triazabicyclo[4.4.0]dec-5-ene	9	82
Comp. 20	2-acetylfuran	sodium isopropoxide	9	60
49	2-methoxyacetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	9	75
Comp. 21	2-methoxyacetophenone	sodium isopropoxide	9	51
50	3',5'-bis(trifluoromethyl)-acetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	9	76
Comp. 22	3',5'-bis(trifluoromethyl)-acetophenone	sodium isopropoxide	12	78

[100] These Examples show that for many ketones, when using ethylene diamine as the achiral diamine ligand, an alkylguanidine base can provide significantly greater enantioselectivity than a basic salt like sodium isopropoxide. They also show that the degree of the relative improvement can also depend on the identity of the ketone.

Examples 51-56 and Comparative Examples 23-28

[101] These Examples show the hydrogenation of various ketones using either 1,5,7-triazabicyclo[4.4.0]dec-5-ene (the Examples) or sodium isopropoxide (the Comparative Examples) in combination with *R*-propylenediamine as the bidentate amine ligand.

[102] The procedure was identical to Example 1 with the exceptions that 625 micromole of the ketone shown in Table 8 was reacted instead of the acetophenone, an equimolar amount *R*-propylenediamine was substituted for the ethylenediamine, an equimolar amount of either 1,5,7-triazabicyclo[4.4.0]dec-5-ene or sodium isopropoxide was substituted for the tetramethyl-2-t-butylguanidine, and the reaction mixture was stirred under hydrogen for the time shown in Table 8. In each example, the analysis showed the conversion of the ketone was 100% and that the chirality of the product alcohol was predominantly *S*. Table 8 gives the ketone base, the reaction time, and the enantiomeric excess of the *S*-alcohol product.

Table 8				
Example	**ketone**	**base**	**Time (hrs)**	**e.e. (%)**
51	acetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	87
Comp. 23	acetophenone	sodium isopropoxide	9	68
52	2-acetylthiophene	1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	93
Comp. 15	2-acetylthiophene	sodium isopropoxide	6	77
53	2'-acetonaphthone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	87
Comp. 24	2'-acetonaphthone	sodium isopropoxide	9	77
54	2-acetylbenzothiophene	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	88
Comp. 25	2-acetylbenzothiophene	sodium isopropoxide	12	81
55	2-acetylfuran	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	87
Comp. 26	2-acetylfuran	sodium isopropoxide	9	74
55	2-methoxyacetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	81
Comp. 27	2-methoxyacetophenone	sodium isopropoxide	9	60
56	3',5'-bis(trifluoromethyl)-acetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	79
Comp. 28	3',5'-bis(trifluoromethyl)-acetophenone	sodium isopropoxide	12	78

[103] These Examples show that for many ketones, when using *R*-propylenediamine as the achiral diamine ligand, an alkylguanidine base can provide significantly greater enantioselectivity than a basic salt like sodium isopropoxide. They also show that the degree of the relative improvement can also depend on the identity of the ketone.

Examples 57-67 and Comparative Examples 29-33

[104] These Examples show the hydrogenation of various ketones using either an alkylguanidine base (the Examples) or sodium isopropoxide (the Comparative Examples) in combination with *meso*-cyclohexanediamine as the bidentate amine ligand.

[105] The procedure was identical to Example 7 with the exceptions that 625 micromole of the ketone shown in Table 9 was reacted instead of the acetophenone, in some reactions an equimolar amount of either 1,5,7-triazabicyclo[4.4.0]dec-5-ene or sodium isopropoxide was substituted for the tetramethyl-2-t-butylguanidine, and the reaction mixture was stirred under hydrogen for the time shown in Table 9. In each example, the chirality of the product alcohol was predominantly *S*. Table 9 gives the ketone base, the reaction time, the conversion of the ketone and the enantiomeric excess of the *S*-alcohol product.

Table 9					
Example	ketone	base	Time (hrs)	Conv. (%)	e.e. (%)
57	acetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	100	73
7	acetophenone	tetramethyl-2-t-butylguanidine	12	100	71
Comp. 7	acetophenone	sodium isopropoxide	6	100	67
26	2-acetylthiophene	1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	56	90
14	2-acetylthiophene	tetramethyl-2-t-butylguanidine	4	84	90
Comp. 14	2-acetylthiophene	sodium isopropoxide	4	100	81
58	2-acetonaphthone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	100	81
59	2-acetonaphthone	tetramethyl-2-t-butylguanidine	12	100	80
Comp. 29	2-acetonaphthone	sodium isopropoxide	9	100	78
60	2-acetylbenzothiophene	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	100	93
61	2-acetylbenzothiophene	tetramethyl-2-t-butylguanidine	12	100	92
Comp. 30	2-acetylbenzothiophene	sodium isopropoxide	12	100	89
62	2-acetylfuran	1,5,7-triazabicyclo[4.4.0]dec-5-ene	9	84	83
63	2-acetylfuran	tetramethyl-2-t-butylguanidine	12	100	83
Comp. 31	2-acetylfuran	sodium isopropoxide	9	100	79
64	2-methoxyacetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	100	71
65	2-methoxyacetophenone	tetramethyl-2-t-butylguanidine	8	84	67
Comp. 32	2-methoxyacetophenone	sodium isopropoxide	9	100	55
66	3',5'-bis(trifluoromethyl)-acetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	100	64
67	3',5'-bis(trifluoromethyl)-acetophenone	tetramethyl-2-t-butylguanidine	12	100	64
Comp. 33	3',5'-bis(trifluoromethyl)-acetophenone	sodium isopropoxide	12	100	70

[106] These Examples show that for many ketones, when using *meso*-cyclohexanediamine as the achiral diamine ligand, an alkylguanidine base can provide greater enantioselectivity than a basic salt like sodium isopropoxide. They also show that the relative improvement can also depend on the identity of the ketone.

Examples 68-73 and Comparative Examples 34-39

[107] These Examples illustrate the hydrogenation of 2-acetylthiophene to 1-(2-thienyl)ethanol using various chiral diphosphine ligands in combinations with ethylenediamine as the bidentate amine ligand and either tetramethyl-2-t-butylguanidine (the Examples) or sodium isopropoxide (the Comparative Examples) as the base.

[108] Stock solutions of [$RuCl_2$(diphosphine)(DMF)n] complexes were prepared by the procedure described for [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n] in Preparation 1. The procedure for the hydrogenation reactions was identical to Example 8 with the exceptions that an equal molar amount the [$RuCl_2$(diphosphine)(DMF)n] having the diphosphine shown in Table 10 (abbreviations are given in the Detailed Description of the Invention) was substituted for [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n], for the Comparative Examples an equimolar amount of sodium isopropoxide was substituted for the tetramethyl-2-t-butylguanidine and the reaction mixtures were stirred for the time shown in Table 10. Table 10 gives the diphosphine, the base, the reaction time, the conversion of the 2-acetylthiophene, the absolute configuration of the 1-(2-thienyl)ethanol, and its e.e.

Table 10

Example	diphosphine	Base	Time (hrs)	Conv. (%)	e.e.(%) (*R*/*S*)
8	*R*,*R*,*R*,*R*-BICP	tetramethyl-2-t-butylguanidine	4	100	86 (*S*)
Comp. 8	*R*,*R*,*R*,*R*-BICP	Sodium isopropoxide	4	100	56 (*S*)
68	*S*,*S*-CHIRAPHOS	tetramethyl-2-t-butylguanidine	8	17	64 (*S*)
Comp. 34	*S*,*S*-CHIRAPHOS	Sodium isopropoxide	12	100	43 (*R*)
69	*R*,*R*-SKEWPHOS	tetramethyl-2-t-butylguanidine	8	29	55 (*S*)
Comp. 35	*R*,*R*-SKEWPHOS	Sodium isopropoxide	6	100	53 (*S*)
70	*R*,*R* -Me-PennPhos	tetramethyl-2-t-butylguanidine	8	49	61 (*S*)
Comp. 36	*R*,*R* -Me-PennPhos	Sodium isopropoxide	12	100	36 (*S*)
71	*R* –BINAP	tetramethyl-2-t-butylguanidine	6	21	23 (*S*)
Comp. 37	*R* –BINAP	Sodium isopropoxide	4	100	23 (*S*)
72	*R* -C4-TunaPhos	tetramethyl-2-t-butylguanidine	12	69	12 (*R*)
Comp. 38	*R* -C4-TunaPhos	Sodium isopropoxide	6	100	3 (*R*)
73	*S* -MeOBIPHEP	tetramethyl-2-t-butylguanidine	12	54	<1 (*R*)
Comp. 39	*S* -MeOBIPHEP	Sodium isopropoxide	6	100	<1 (R)

[109] These Examples show that for many chiral diphosphines, when using ethylenediamine as the bidentate amine ligand, an alkylguanidine base can provide greater enantioselectivity than a basic salt like sodium isopropoxide. They also show that the improvement can also depend on the identity of the chiral diphosphine. Among these chiral diphosphines, the greater such improvements as well as the greater absolute enantioselectivities are obtained among the nonatropisomeric chiral diphosphines (Examples 8, 69, and 70), while the lesser such improvements and lesser absolute enantioselectivities are obtained among the atropisomeric chiral diphosphines (Examples 71, 72, and 73).

[110] Examples 68 and Comparative Example 34, using CHIRAPHOS show the surprising result of the chirality of the dominant enantiomer of the nonracemic alcohol being switched upon using the tetramethyl-2-t-butylguanidine instead of sodium isopropoxide.

Examples 74-80 and Comparative Examples 40-46

[111] These Examples illustrate the hydrogenation of 2-acetylthiophene to 1-(2-thienyl)ethanol using various chiral diphosphine ligands in combinations with *meso*-cyclohexanediamine as the bidentate amine ligand and either tetramethyl-2-t-butylguanidine (the Examples) or sodium isopropoxide (the Comparative Examples) as the base.

[112] The procedure was identical to Example 14 with the exceptions that an equal molar amount the [$RuCl_2$(diphosphine)(DMF)n] having the diphosphine shown in Table 10 (abbreviations are given in the Detailed Description of the Invention) was substituted for [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n], for the Comparative Examples an equimolar amount of sodium isopropoxide was substituted for the tetramethyl-2-t-butylguanidine and the reaction mixtures were stirred for the time shown in Table 11. Table 11 gives the diphosphine, the base, the reaction time, the conversion of the 2-acetylthiophene, the absolute configuration of the 1-(2-thienyl)ethanol, and its e.e.

[113] These Examples show that, when using *meso*-cyclohexanediamine as the bidentate amine ligand, the greater enantioselectivities are obtained when using the preferred nonatropisomeric chiral diphosphine ligands (Examples 14, 74-77) as compared to the atropisomeric chiral diphosphine ligands (Examples 78-80). The Examples using the most preferred chiral diphosphine ligands, comprising four stereogenic carbon atoms in the hydrocarbyl diradical that connects the two phosphorus atoms (Examples 14 and 74) show substantial improvements in enantioselectivity using tetramethyl-2-t-butylguanidine as compared to using sodium isopropoxide. Examples 74 and Comparative Example 40, using CHIRAPHOS show the surprising result of the chirality of the dominant enantiomer of the nonracemic alcohol being switched upon using the tetramethyl-2-t-butylguanidine instead of sodium isopropoxide. A similar switch in chirality, though lesser in e.e. points, is shown by Examples 79 and Comparative Example 45, using *R* -C4-TunaPhos. For a number of the other chiral diphosphines, the enantioselectivity with tetramethyl-2-t-butylguanidine was no better than that with sodium isopropoxide. The data in Tables 10 and 11, collectively, show that the enantioselectivity advantages which may be provided by the alkylguanidine bases in the present invention is dependent on both the diphosphine

ligand and the bidentate amine ligand, and can be determined by routing experimentation.

Table 11

Example	diphosphine	base	Time (hrs)	Conv. (%)	e.e.(%) (*R/S*)
14	*R,R,R,R*-BICP	tetramethyl-2-t-butylguanidine	4	84	90 (*S*)
Comp. 14	*R,R,R,R*-BICP	sodium isopropoxide	4	100	81 (*S*)
74	*S,S*-CHIRAPHOS	tetramethyl-2-t-butylguanidine	8	18	64 (*S*)
Comp. 40	*S,S*-CHIRAPHOS	sodium isopropoxide	10	100	58 (*R*)
75	*R,R*-SKEWPHOS	tetramethyl-2-t-butylguanidine	8	10	52 (*S*)
Comp. 41	*R,R*-SKEWPHOS	sodium isopropoxide	12	90	56 (*S*)
76	*R,R* -Me-PennPhos	tetramethyl-2-t-butylguanidine	8	63	77 (*S*)
Comp. 42	*R,R* -Me-PennPhos	sodium isopropoxide	12	100	76 (*S*)
77	*R,R*-DIOP	tetramethyl-2-t-butylguanidine	8	5	52 (*R*)
Comp. 43	*R,R*-DIOP	sodium isopropoxide	12	94	57 (*R*)
78	*R* –BINAP	tetramethyl-2-t-butylguanidine	6	12	34 (*S*)
Comp. 44	*R* –BINAP	sodium isopropoxide	4	100	45 (*S*)
79	*R* -C4-TunaPhos	tetramethyl-2-t-butylguanidine	12	25	24 (*R*)
Comp. 45	*R* -C4-TunaPhos	sodium isopropoxide	6	100	33 (*S*)
80	*S* -MeOBIPHEP	tetramethyl-2-t-butylguanidine	12	20	34 (*R*)
Comp. 46	*S* -MeOBIPHEP	sodium isopropoxide	10	100	41 (*R*)

Examples 81-83 and Comparative Examples 47-49

[114] These Examples show the hydrogenation of 3-(dimethylamino)-1-(2-thienyl)1-propanone to nonracemic 3-(dimethylamino)-1-(2-thienyl)1-propanol using various diamine ligands and either tetramethyl-2-t-butylguanidine (the Examples) or sodium isopropoxide (the Comparative Examples) as the base.

[115] A 1.47 mM solution of [$RuCl_2$((*R,R,R,R*-BICP)(DMF)n] in isopropanol was prepared from [$RuCl_2$(benzene)]$_2$ and 1.1 equivalents *R,R,R,R*-BICP following the general procedure given in Preparation 1. For each example, in a dry nitrogen-filled glovebox, a 20-ml glass reaction vial was charged with 2 mL 1.47 mM (2.9 micromole) [$RuCl_2$((*R,R,R,R*-BICP)(DMF)n] in isopropanol, 3 mL isopropanol, 0.58 mL 0.1M (0.58 mmole) diamine ligand in isopropanol, 0.25 g (1.43 mmole) 3-(dimethylamino)-1-(2-thienyl)1-propanone (free base), and 0.29mL 0.2M (0.58 mmole) base in isopropanol. The glass reaction vial containing the resulting mixture was sealed in an autoclave, which was then removed from the glovebox. The gas phase in the autoclave was replaced by hydrogen and the reaction mixture was stirred under 6.8 bar (gauge) hydrogen at room temperature for 18 hours. The reaction mixture was

sampled and analyzed by chiral HPLC. was 100%. Table 12 gives the achiral diamine ligand, the base, the conversion of the ketone, and the enantiomeric excess of the resulting *S*-3-(dimethylamino)-1-(2-thienyl)1-propanol product.

Example	diamine ligand	base	Conv. (%)	e.e. (%)
81	ethylene diamine	tetramethyl-2-t-butylguanidine	89	79
Comp. 47	ethylene diamine	sodium isopropoxide	96	24
82	2-methyl-1,2-propylenediamine	tetramethyl-2-t-butylguanidine	85	85
Comp. 48	2-methyl-1,2-propylenediamine	sodium isopropoxide	97	68
83	meso-1,2-cyclohexanediamine	tetramethyl-2-t-butylguanidine	77	88
Comp. 49	meso-1,2-cyclohexanediamine	sodium isopropoxide	96	83

[116] These Examples further show that an alkylguanidine base can provide significantly greater enantioselectivity than a basic salt like sodium isopropoxide in the process of the invention. They also show that the degree of the relative improvement can also depend on the identity of the diamine ligand, and appears greatest with a simpler and smaller achiral diamine, especially with ethylene diamine.

Examples 83-90

[117] These Examples illustrate the inventive process for hydrogenation of 3',5'-bis(trifluoromethyl)acetophenone to nonracemic 3',5'-bis(trifluoromethyl)-1-phenethanol in various solvents using tetramethyl-2-t-butylguanidine as the base. They also illustrate the use of an amino-thioether as the bidentate amine ligand in the present invention.

[118] Stock solutions of 556 micromolar [$RuCl_2$((*R*,*R*,*R*,*R*-BICP)(DMF)n] in various anhydrous, deaerated solvents were prepared analogous to the procedure in Preparation 1 by dissolving the solid residue comprising [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n] in the desired solvent instead of isopropanol. In the same manner as described in Example 1, solutions prepared from 0.2843 g (1.11 mmol) 3',5'-bis(trifluoromethyl)acetophenone, 10 mL 556 micromolar (5.56 micromoles) [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n] in the solvent, 0.22 mL 0.1 M (22 micromole) 2-(ethylthio)aniline in the solvent, and 0.20 mL 0.1 M (20 micromoles) tetramethyl-2-t-butylguanidine in the solvent were stirred under 100 psi hydrogen for 19 hours at room temperature. Table 13 gives the solvent, the conversion of the 3',5'-bis(trifluoromethyl)acetophenone, and the e.e of the (*S*)-3',5'-bis(trifluoromethyl)-1-phenethanol product.

Table 13			
Example	solvent	Conv. (%)	%e.e.
83	isopropanol	100	72
84	toluene	100	77
85	dibutyl ether	100	75
86	dichloromethane	100	75
87	chlorobenzene	100	78
88	ethylacetate	37	74
89	1,2-dimethoxy ethane	58	78
90	methyl t-butyl ether	24	70

[119] These results show that that an organic base selected from alkylamidines, alkylguanidines, aminophosphazenes, and proazaphosphatranes allows the inventive process to be conducted using solvents other than alcohol solvents and in which basic salts such as sodium isopropoxide are not soluble, and that many solvents provide for higher enantioselectivities than the alcohol solvent.

[120] Examples 84 and 86 may be compared to the report in *J. Am. Chem. Soc.*, vol. 117 (1995), 2675-2676 that toluene and dichloromethane are not useable in the disclosed process using KOH or $(CH_3)_2CHOK$ as the base.

Examples 91-99 and Comparative Examples 50-52

[121] These Examples illustrate the process of the invention for the hydrogenation of a enantiomeric chiral ketone to a diastereomeric chiral alcohol. The Comparative Examples show results obtained using certain organic bases that are not selected from alkylamidines, alkylguanidines, aminophosphazenes, and proazaphosphatranes.

[122] For each example, (2*S*)-1-(4-benzyl-oxy-phenyl)-2-(4-hydroxy-4-phenyl-piperidin-1-yl)-1-propanone was hydrogenated in isopropanol solution at room temperature under 18 bar hydrogen for four hours using $[RuCl_2((S,S,S,S\text{-BICP})(DMF)n]$, 4,5-dimethyl-1,2-diamino-benzene and a base in the mole ratios ketone:RuBICP:diamine:base = 500:1:5:20. The reaction mixture was analyzed by chiral HPLC. Table 14 gives the base, the conversion of the ketone and the chemical yield of the (1*S*,2*S*)-diastereomer of 1-(4-benzoxyphenyl)2-(4-hydroxy-4-phenyl-piperidin-1-yl)-1-propanol.

Example	base	Conv. (%)	yield (%)
Comp. 50	guanidine	1.4	1.4
Comp. 51	4,7,13,16,21-pentaoxa-1,10-diazabicyclo[8.8.5]tricosane	0.1	0.1
Comp. 52	sodium isopropoxide	98.6	93.2
91	N'''-[N-ethyl-P,P-bis(dimethylamino)phosphinimyl]-N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide	99.5	95.1
92	N'''-*t*-butyl-N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide	99.5	96.5
93	N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide	99.6	95.2
94	t-butyl-tris[tris(dimethylamino)phosphoranylidene]phosphorimidic triamide	99.6	96.4
95	2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane	98.6	93.2
96	1,5,7-triazabicyclo[4.4.0]dec-5-ene	99.6	96.2
97	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	99.5	96.7
98	tetramethyl-2-t-butylguanidine	99.5	97.1
99	tetramethylguanidine	60.7	58.8

[123] Examples 91-99 show that organic bases selected from alkylamidines, alkylguanidines, aminophosphazenes, and proazaphosphatranes provide high activity and diastereoselectivity in the process of the invention. Comparative Examples 50 and 51 show that certain other organic bases provide insignificant catalytic activity. By comparison to Comparative Example 50 using guanidine, Examples 98 and 99 show that the N-alkyl substitution in the alkylguanidine bases is required for catalyst system activity. Comparative Example 50 shows that a trialkylamine base does not provide any significant catalyst activity.

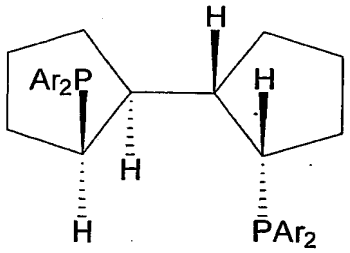
[124] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. Catalyst system useful for the hydrogenation of a ketone to a nonracemic chiral alcohol comprising ruthenium, a nonracemic chiral diphosphine ligand, a bidentate amine ligand, and an organic base selected from alkylamidines, alkylguanidines, aminophosphazenes, and proazaphosphatranes, with the proviso that when said nonracemic chiral diphosphine is an atropisomeric diphosphine and the organic base is selected from alkylamidines, said catalyst system is essentially free of alkali metal salt.

2. Catalyst system according to claim 1 wherein the nonracemic chiral diphosphine ligand is a nonracemic nonatropisomeric chiral diphosphine ligand, preferably a nonracemic nonatropisomeric chiral diphosphine ligand comprising at least one stereogenic carbon atom, more preferably a nonracemic nonatropisomeric chiral diphosphine ligand comprising at least one stereogenic carbon atom in a hydrocarbyl diradical that connects the two phosphorus atoms.

3. Catalyst system according to claim 1 or claim 2 wherein the nonracemic nonatropisomeric diphosphine ligand comprises a 2,2'-bis(diorganophosphino)-1,1'-bis(cyclic) structure, preferably nonracemic nonatropisomeric diphosphine ligand selected from enantiomers of diphosphine ligands having the structural formula



wherein Ar is an aryl group.

4. Catalyst system according to claim 3 wherein Ar is selected from phenyl, monoalkylphenyl, dialkylphenyl, and trialkylphenyl.

5. Catalyst system according to any of claims 1-4 wherein the bidentate amine ligand is a diamine ligand, preferably a bis-primary amine ligand, more preferably an achiral diamine ligand, most preferably a diamine ligand

selected from *meso*-1,2-alkylenediamine compounds, 1,2-phenylenediamine compounds and 1,8-diaminonaphthalene compounds.

6. Catalyst system according to any of claims 1-4 wherein the bidentate amine ligand is an amino-thioether ligand, preferably an amino-thioether ligand selected from 2-(alkylthio)ethylamines and 2-(alkylthio)anilines, more preferably the amino-thioether is a 2-(alkylthio)aniline.

7. Catalyst system according to any of claims 1-6 wherein the organic base is selected from alkylguanidines, aminophosphazenes, and proazaphosphatranes, preferably the organic base is an alkylguanidine, more preferably the organic base is selected from tetraalkylguanidines and pentaalkylguanidines.

8. Process for the preparation of a nonracemic chiral alcohol comprising hydrogenating a ketone in the presence of a catalyst system according to any of claims 1-7.

9. Process according to claim 8 wherein the nonracemic chiral alcohol is formed in at least about 60% stereomeric excess.

INTERNATIONAL SEARCH REPORT

PCT/NL 02/00827

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J31/24 B01J31/18 C07F15/00 C07D239/00 C07F9/06
C07F9/6584 C07C257/10 C07C279/04 C07C279/16 C07C29/145
C07B53/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J C07F C07C C07B C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HARTMANN R ET AL: "NOYORI'S HYDROGENATION CATALYSTS NEEDS A LEWIS ACID COCATALYST FOR HIGH ACTIVITY" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 40, no. 19, 1 October 2001 (2001-10-01), pages 3581-3585, XP001111827 ISSN: 0570-0833 cited in the application the whole document	1,5,8,9
P,X	WO 02 055195 A (CHEN PETER ;THALES TECHNOLOGIES AG (CH)) 18 July 2002 (2002-07-18) page 18 -page 20 page 16, line 3-14; claims 44-52,71-78 examples	1-3,5,8, 9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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